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EXAMINER
HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/270,910	Applicant(s) IPSEN ET AL.	
	Examin r Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication app ars on the cover she t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication:
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-9,12-14,19,24-26,28-34 and 40-51* is/are pending in the application.

4a) Of the above claim(s) *29-31 and 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5-9,12-14,19,24-26,28,32-34, 47-49 and 51* is/are rejected.

7)☒ Claim(s) *50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 2-3, 5-9, 12-14, 19, 24-26, 28-34 and 40-51 are pending.

2. Claims 29-31 and 40-46 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected inventions.

3. In view of the amendment filed 2/27/03, the following rejections remain.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2-3, 5-9, 12-14, 19, 24-26, 28, 32-34, 47-49 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a recombinant mutant allergen from birch pollen major allergen of SEQ ID NO: 37 having one or more amino acid substitutions such as the ones disclosed on page 27 lines 25-32 or the ones recited in claim 50 and (2) a recombinant mutant allergen from Ves v 5 of SEQ ID NO: 38-39 having one or more amino acid substitutions such as the ones disclosed on page 44-46 obtainable by the method recited in claim 2 for treating allergic reactions, **does not** reasonably provide enablement for (1) *any* recombinant mutant allergen derived from *any* naturally occurring allergen in which at least one surface-exposed, *any* amino acid residue of a B cell epitope at *any* position which is conserved in *any* amino acid sequences of *any* homologous proteins within the taxonomic order from which the naturally occurring allergen originates, is substituted with *any* amino acid residue which is not conserved in the same position in the amino acid sequences of any homologous proteins within the taxonomic order from which the naturally occurring allergen originates, wherein the α-carbon backbone tertiary structure of *any* naturally occurring allergen, and specific IgE binding to *any* mutant allergen is reduced compared to the IgE binding to *any* naturally occurring allergen, (2) *any* recombinant allergen mentioned above obtainable by a) identifying *any* amino acid residues in *any* naturally occurring allergen which are conserved with more than 70% identity in all known homologous proteins within the taxonomic order from which said naturally occurring allergen originates, (b) defining at least one patch of conserved amino acid residues being coherently

connected over at least 400 $Å^2$ of the surface of the thee-dimensional structure of *any* naturally occupying allergen molecule as defined by having a solvent accessibility of at least 20%, said at least one patch comprising at least one B cell epitope and (c) substituting at least *any* one amino acid residue in said *any* one patch with another non-conservative amino acid, wherein the α-carbon backbone tertiary structure of the allergen molecule is conserved, (3) *any* recombinant allergen mentioned above wherein the specific IgE binding to the mutant allergen is reduced by at least 5%, preferably by at least 10%, (4) *any* recombinant allergen mentioned above wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of *any* mutant and the naturally occurring allergen molecules is below 2 Å, (5) *any* recombinant allergen obtainable by the process of claim 2 wherein said at least *any* one patch consisting of *any* 15 amino acid residues, (6) *any* recombinant allergen obtainable by the process of claim 2 wherein the amino acid residues of *any* one patch are ranked with respect to solvent accessibility and *any* one or more amino acids among the more solvent accessible ones are substituted, (7) *any* recombinant allergen mentioned above wherein one or more amino acid residues of *any* one patch having a solvent accessibility of 20-80% are substituted, *any* 1-5 amino acids residues per 400 $Å^2$ in any one patch are substituted, *any* substitution of one or more amino acid residues in any B cell epitope or *any* one patch is carried out by site-directed mutagenesis, (8) *any* recombinant allergen mentioned above wherein the allergen is derived from *any* inhalation allergen, *any* pollen allergen, *any* pollen allergen originating from the taxonomic order of Fagales, Oleales or inales, (9) *any* recombinant allergen derived from Bet v1 wherein at least *any* one amino acid residues of said B cell epitope or said at least *any* one patch is substituted, (10) *any* recombinant allergen mentioned above derived from inhalation allergen wherein the allergen is a pollen allergen derived from *any* pollen allergen originating from the taxonomic order of Poales, Asterales, or Urticales, house dust mite, mite allergen from Dermatophagoides, cockroach allergen, *any* animal allergen such as the ones from cat, dog or horse, venom allergen originating from the taxonomic order of Hymenoptera, Vespidae, Apidae and Formicoidae, *any* allergen derived from Ves v5 (11) *any* recombinant allergen wherein the allergen is derived from any venom allergen wherein at least one amino acid is substituted such as the substitution is from Lys to Ala at position 72 or from Tyr to Ala at position 96, (12) *any* recombinant allergen mentioned above for use as a pharmaceutical, (13) *any* pharmaceutical composition comprising *any* recombinant allergen mentioned above optionally in combination with *any* pharmaceutical acceptable carrier and/or excipient, and optionally an adjuvant, (14) *any* pharmaceutical

composition mentioned above in the form of a vaccine against allergic reactions elicited by any naturally occurring allergen in patients suffering from allergy, (15) *any* pharmaceutical composition obtainable by the process such as the process recited in claim 48, and (16) *any* recombinant allergen obtainable by the process recited in claim 2 wherein said at least one patch consists of at least *any* 15 amino acid residues, or *any* 15-25 amino acid residues for a vaccine.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two recombinant allergens from birch pollen major allergen comprising SEQ ID NO: 37 from the taxonomic order of *Fagales* and vaspid venom Ves v 5 comprising SEQ ID NO: 38-39 from the taxonomic order of Hymenoptera. The specification discloses recombinant mutant allergen from birch pollen major allergen comprising SEQ ID NO: 37 wherein said allergen has one or more amino acid substitutions such as the ones disclosed on page 27 lines 25-32 of the specification or the ones recited in claim 50. The specification further discloses recombinant mutant allergen from vaspid venom Ves v 5 comprising SEQ ID NO: 38-39 having one or more amino acid substitutions such as the ones disclosed on page 44-46. The said recombinant mutant allergens obtainable by the method recited in claim 2 for treating allergic reactions.

Other than the specific amino acid substitutions in the specific allergens of SEQ ID NO: 37-39 mentioned above, the specification does not teach how to make and use *any* recombinant mutant allergen such as inhalation allergen from the taxonomic order of *Oleales*, *Pinales*, *Asterales*, *Urticales*, allergen from a house dust mite originating from *Dermatophagoides*, cockroach allergen, or animal allergen originating from a cat, dog or horse in which at least one surface-exposed amino acid residues of any B cell epitope at any position which is conserved in

the amino acid sequences of homologous proteins within the taxonomic order from which the naturally occurring allergen originates is substituted with *any* amino acid residue which is not conserved in the same position wherein the recombinant mutant allergen has an α-carbon backbone tertiary structure essentially the same as the α-carbon backbone tertiary structure of the naturally occurring allergen and specific IgE binding to the mutant allergen is reduced compared to the IgE binding to the naturally occurring allergen wherein the specific IgE binding to the mutant is reduced by at least 5%, preferably at least 10% wherein at least one patch of conserved amino acid residues comprises atoms of 15-25 amino acid residues ranked with respect to solvent accessibility and one ore more amino acids among the more solvent accessible ones are substituted for a pharmaceutical composition or a vaccine.

There is insufficient guidance and working example as to which amino acid residues within the B cell epitope such as any patch of amino acid residues consisting of at least 15 amino acids or 15-25 amino acid residues in length of any inhale allergen from any taxonomic order such as *Oleales*, *Pinales*, *Asterales*, *Urticales*, allergen from a house dust mite originating from *Dermatophagoides*, cockroach allergen, or animal allergen originating from a cat, dog or horse that can be substitute and whether after amino acid substitutions would maintain the α-carbon backbone tertiary structure and reduced IgE binding at least 5%, or at least 10% as compared to the naturally occurring allergen, in turn, would be useful for a pharmaceutical composition or a vaccine against any allergen. It is well known in the art that the relationship between the sequence of a protein and its tertiary structure (i.e. its binding activity) are not well understood and are not predictable (see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz, et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495).

The state of the prior art as exemplified by Lebecque *et al*, Gajhede *et al* and Elsayed *et al* (all of record) is such that determining the IgE binding of Bet v 1 (B cell epitope) is conformational dependent by nature, including applicants' disclosure on page 36 bridging to page 37. Given the diversity of B cell epitope ranging from conformational to linear epitope structures, there is no predictability regarding what effect amino acid substitutions will have on the structure and function of all allergen to which the antibody binds because it is difficult to predict the 3-D structure of modified allergens from a primary structure such as amino acid sequence alignment, in turn, would be useful for a vaccine against all allergy. The predictability of making modified allergens mentioned above is limited to factors such as the mutagenesis method. Given the insufficient guidance and working examples, predicting what changes can be

made to the amino acid sequence of any allergen mentioned above that after substitution, will retain both structure and reduce IgE function *in vivo* is unpredictable. Since the specification fails to provide guidance regarding which amino acid can tolerate change, it follows that any allergen mentioned above other than Bet v I from the taxonomic order of *Fagales* and vaspid venom Ves v 5 from the taxonomic order of Hymenoptera is not enable.

With regard to a pharmaceutical composition and vaccine comprising any recombinant mutant allergen, there are no in vivo working example demonstrating any recombinant mutant allergen mentioned above is effective in prevent any allergy. There are no showing of any recombinant mutant allergen mentioned above, other than Bet v 1 and Ves v 5, that reduce IgE binding for the specific allergies. Even if IgE binding is reduced by 5% or by 10%, there is still a 95% or 90% chance that the mutant allergen could bind IgE and induce anaphylaxis. A vaccine in the absence of in vivo data is unpredictable for the following reasons: (1) the recombinant mutant allergen may increase IgE production and binding, (2) the recombinant mutant allergen may be inactivated before producing an effect, for instant, due to proteolytic degradation or immunological inactivation as a consequence of the inherently short half-life, this led to a lack of allergen specific antibody production; (3) other functional properties, known or unknown, may make the recombinant mutant allergen unsuitable for in vivo therapeutic use, i.e. such as adverse side effects of unwanted immune suppression that prohibit the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In view of the quantity of experimentation necessary, the lack of in vivo working examples, the unpredictability of the art, the insufficient guidance with respect to the appropriate modifications within the full-length polypeptide of any allergen from any taxonomic order and the breadth of the claims, one skilled in the art could not use the claimed invention without undue amount of experimentation.

Applicants' arguments filed 2/27/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention is based on the discovery that substituting amino acids in surface accessible portions of allergens reduces the IgE binding to the allergen by a sufficient degree (at least 5%) to provide a better immunotherapeutic protein. Applicants assert that the specification enables the full scope of these claims. The claimed invention is directed to recombinant allergens derived from naturally occurring allergens from the taxonomic orders Fagales, Hymenoptera or Dermatophagoides wherein a conserved surface-

exposed amino acid is mutated to non-conserved amino acid which retains the α-carbon backbone tertiary structure of the naturally occurring allergen and has a reduced specific IgE binding compared to natural allergen. (2) at the filing date of the application, it was routine to identify homologous allergens, including homologous allergens from the taxonomic orders Fagales, Hymenoptera or Dermatophagoides, and identity of conserved amino acids in the homologous allergens using commercially available alignment programs, (See King Declaration submitted on April 10, 2002). The specification at page 24-25, bridging paragraph, set forth the example of using BLAST to identify sequence homology to Bet v1. One of ordinary skill in the art would have further been able to determine which of the conserved amino acids identified using the methods described above is a surface-exposed amino acid residue of a B cell epitope, the specification at page 17, lines 29-31 sets forth that the α-carbon backbone is best determined either before or after matagenesis, by X-ray crystallography or NMR, both of which were established routine technologies. Following the identification of the surface-exposed amino acids of even a single member of a family of homologous allergens, the alignment procedures discussed supra allow the identification of the conserved surface-exposed amino acids of any other homologous allergen. The criteria for choosing which amino acids are B-cell epitopes that are to be substituted are set forth in page 14-15. It is unlikely that a single amino acid substitution at a solvent accessible position would have any effect on the α-carbon backbone structure. Lastly, the specification set forth that IgE binding can be determined using a fluid-phase IgE-inhibition assay using the pool of serum IgE derived from allergic patients (page 34, lines 15-18). (2) Applicants have reduced the claimed invention to practice using two unrelated allergens from different taxonomic orders, two working examples of two different recombinant allergens as claimed, (3) the claims have been restricted to allergens originated from the taxonomic orders Fagales, Hymeoptera or Dermatophagoides. (3) The specification gives extensive guidance in identifying and alignment of identifying and aligning allergen homologous. (4) With regard to pharmaceutical composition and vaccine, it is well accepted that vaccination using allergens from natural sources has an inherent risk of side effects due to allergen specific IgE binding. To overcome the possible side effects associated with allergen vaccines, it has been desirable to produce allergen vaccines with reduced IgE binding. The Examiner has failed to provide any credible evidence to the contrary. (5) Even a 5% reduction in IgE binding increases the value of the mutant allergen in immunotherapy. (6) The claimed recombinant allergens bear one or more point mutations but retain the tertiary structure of the original allergen. (7) Branden et al supports

Applicants' position that the specification is enabling with regard defining B cell epitopes on any allergen that is a member of a homologous allergen family wherein the tertiary structure has been determined for even one member of the allergen family. (8) Abaza et al's teaching that amino acid substitutions outside the protein antigenic site can exert drastic effects on the reactivity of a monoclonal antibody against the site is of limited, if any, relevance. The claims are directed to recombinant mutant allergens with substitution within an antigenic site. (9) Lederman et al's teaching that even a single amino acid substitution can ablate the binding of a monoclonal antibody to a protein supports Applicants' position that following the procedures set forth in the specification would enable one of ordinary skill in the art to obtain recombinant allergens with mutations in the IgE epitopes that reduce IgE binding. (10) Those of ordinary skill in the art routinely and predictably perform each of the methods required to practice the claimed invention. (11) Little of no experimentation is required to enable one of ordinary skill in the art to practice the claimed invention.

However, the claims are drawn to *any* recombinant allergen from *any* one of the taxonomic orders such as Fagales, Hymernoptera and Dermatophagoides having *any* point mutation or *any* amino acid substitution in *any* patch of at least 15 amino acids in *any* undisclosed allergens from said taxonomic orders such as Fagales, Hymernoptera and Dermatophagoides.

The specification discloses only two recombinant allergens from birch pollen major allergen comprising SEQ ID NO: 37 from the taxonomic order of *Fagales* and vaspid venom Ves v 5 comprising SEQ ID NO: 38-39 from the taxonomic order of Hymenoptera. Further, there are no in vivo working examples demonstrating that any recombinant allergens or any recombinant modified allergen from any taxonomic orders are effective in prevent all allergy.

The issue here is whether one skill in the art could predict which undisclosed amino acid or amino acids within the full length amino acid sequence of *any* undisclosed allergen from the taxonomic orders such as Fagales, Hymernoptera and Dermatophagoides could be substitute for which non-conserved amino acid and whether the resulting recombinant allergen reduce IgE binding while the overall α-carbon backbone tertiary structure is preserved. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain IgE binding or functional aspects of any undisclosed allergen and finally what changes can be tolerated with respect thereto is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is

necessary in order to satisfy the statute. X-ray crystallography or NMR spectroscopy requires highly skill in the art to perform. It is outside the realm of routine experimentation to perform X-ray crystallography or NMR for a large number of undisclosed allergen. In the instant application, it is noted that various mutations, substitutions and the like provide a range of activities, not all which are necessarily predictive of reduced IgE binding while the overall α-carbon backbone tertiary structure is preserved, See Fig 7, for example. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities.

The specification merely mentions identifying the common epitopes within all the known Fagales pollen allergen Bet V 1 by sequence alignment. After alignment of all known amino acid sequences in combination with an analysis of the molecular surface of Bet V 1 by the α-carbon backbone tertiary structure, select amino acid residues for site-directed mutagenesis among residues present in Bet V1 and testing for IgE binding.

Other than the specific recombinant allergen mentioned above, there is insufficient guidance as to which amino acid residue within which patch comprising at least one B cell epitope of the full-length amino acid sequence of *any* undisclosed allergen from the taxonomic orders of Fagales, Hymernoptera and Dermatophagoides to be changed to which non-conserved amino acid and whether the resulting recombinant allergen has reduce IgE binding.

Because of the lack of sufficient guidance and predictability in determining which modifications would lead to reduced IgE binding while the overall α-carbon backbone tertiary structure is preserved and that the relationship between the amino acid sequence of a allergen and its tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of the claimed invention.

Skolnick *et al* teach that squence-based methods for function prediction are inadequate and knowing a protein's structure (amino acid sequence) does not necessary tell one it's function (See entire document, Abstract in particular). Attwood *et al* teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable (See figure, entire document). Branden et al (PTO 1449) teaches there are no methods

available today to model a tertiary structure from the amino acid sequence alone and obtain a model detailed enough to be of any use, for example, in drug design and protein engineering (See page 350, in particular). Branden *et al* further teach secondary structure cannot in general be predicted with a high degree of confidence with the possible exceptions of transmembrane helices and α-helical coiled coils (See page 350, in particular). Contrary to Dr. King's position that one of ordinary skill in the art could determine which amino acids and the specific type of amino acid within the full-length amino acid sequence of any recombinant allergen could be substituted, Lederman *et al* teach that even a single amino acid substitution can ablate the binding of the monoclonal antibody to the protein (See abstract, in particular). Abaza *et al* teach amino acid substitution even outside the protein antigenic sites can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the lack of guidance as to which specific amino acid within the B cell epitope (the patch) of any undisclosed allergen mentioned above can tolerate change, it is unpredictable which undisclosed recombinant mutant allergen would reduce binding of IgE by at least 5% or 10% while the α-carbon backbone is preserved, let alone for use as a vaccine against allergic reactions elicited by any naturally occurring allergen in patients suffering from any allergy.

6. Claims 2-3, 5-9, 12-14, 19, 24-26, 28, 32-34, 47-49 and 51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* recombinant mutant allergen derived from *any* naturally occurring allergen in which at least one surface-exposed, *any* amino acid residue of a B cell epitope at *any* position which is conserved in *any* amino acid sequences of *any* homologous proteins within the taxonomic order from which the naturally occurring allergen originates, is substituted with *any* amino acid residue which is not conserved in the same position in the amino acid sequences of any homologous proteins within the taxonomic order from which the naturally occurring allergen originates, wherein the α-carbon backbone tertiary structure of *any* naturally occurring allergen, and specific IgE binding to *any* mutant allergen is reduced compared to the IgE binding to *any* naturally occurring allergen, (2) *any* recombinant allergen mentioned above obtainable by a) identifying *any* amino acid residues in *any* naturally occurring allergen which are conserved with more than 70% identity in all known

homologous proteins within the taxonomic order from which said naturally occurring allergen originates, (b) defining at least one patch of conserved amino acid residues being coherently connected over at least 400 $Å^2$ of the surface of the thee-dimensional structure of *any* naturally occupying allergen molecule as defined by having a solvent accessibility of at least 20%, said at least one patch comprising at least one B cell epitope and (c) substituting at least *any* one amino acid residue in said *any* one patch with another non-conservative amino acid, wherein the α-carbon backbone tertiary structure of the allergen molecule is conserved, (3) *any* recombinant allergen mentioned above wherein the specific IgE binding to the mutant allergen is reduced by at least 5%, preferably by at least 10%, (4) *any* recombinant allergen mentioned above wherein the average root mean square deviation of the atomic coordinates comparing the α-carbon backbone tertiary structures of *any* mutant and the naturally occurring allergen molecules is below 2 Å, (5) *any* recombinant allergen obtainable by the process of claim 2 wherein said at least *any* one patch consisting of *any* 15 amino acid residues, (6) *any* recombinant allergen obtainable by the process of claim 2 wherein the amino acid residues of *any* one patch are ranked with respect to solvent accessibility and *any* one or more amino acids among the more solvent accessible ones are substituted, (7) *any* recombinant allergen mentioned above wherein one or more amino acid residues of *any* one patch having a solvent accessibility of 20-80% are substituted, *any* 1-5 amino acids residues per 400 $Å^2$ in any one patch are substituted, *any* substitution of one or more amino acid residues in any B cell epitope or *any* one patch is carried out by site-directed mutagenesis, (8) *any* recombinant allergen mentioned above wherein the allergen is derived from *any* inhalation allergen, *any* pollen allergen, *any* pollen allergen originating from the taxonomic order of Fagales, Oleales or inales, (9) *any* recombinant allergen derived from Bet v1 wherein at least *any* one amino acid residues of said B cell epitope or said at least *any* one patch is substituted, (10) *any* recombinant allergen mentioned above derived from inhalation allergen wherein the allergen is a pollen allergen derived from *any* pollen allergen originating from the taxonomic order of Poales, Asterales, or Urticales, house dust mite, mite allergen from Dermatophagoides, cockroach allergen, *any* animal allergen such as the ones from cat, dog or horse, venom allergen originating from the taxonomic order of Hymenoptera, Vespidae, Apidae and Formicoidae, *any* allergen derived from Ves v5 (11) *any* recombinant allergen wherein the allergen is derived from any venom allergen wherein at least one amino acid is substituted such as the substitution is from Lys to Ala at position 72 or from Tyr to Ala at position 96, (12) *any* recombinant allergen mentioned above for use as a pharmaceutical, (13) *any* pharmaceutical composition comprising

any recombinant allergen mentioned above optionally in combination with *any* pharmaceutical acceptable carrier and/or excipient, and optionally an adjuvant, (14) *any* pharmaceutical composition mentioned above in the form of a vaccine against allergic reactions elicited by any naturally occurring allergen in patients suffering from allergy, (15) *any* pharmaceutical composition obtainable by the process such as the process recited in claim 48, and (16) *any* recombinant allergen obtainable by the process recited in claim 2 wherein said at least one patch consists of at least *any* 15 amino acid residues, or *any* 15-25 amino acid residues for a vaccine.

The specification discloses only two recombinant allergens from birch pollen major allergen comprising SEQ ID NO: 37 from the taxonomic order of *Fagales* and vaspid venom Ves v 5 comprising SEQ ID NO: 38-39 from the taxonomic order of Hymenoptera. The specification discloses recombinant mutant allergen from birch pollen major allergen comprising SEQ ID NO: 37 wherein said allergen has one or more amino acid substitutions such as the ones disclosed on page 27 lines 25-32 of the specification or the ones recited in claim 50. The specification further discloses recombinant mutant allergen from vaspid venom Ves v 5 comprising SEQ ID NO: 38-39 having one or more amino acid substitutions such as the ones disclosed on page 44-46. The said recombinant mutant allergens obtainable by the method recited in claim 2 for treating allergic reactions.

With the exception of the specific recombinant mutant allergens mentioned above, there is insufficient written description about the structure associated with functions of (1) *any* recombinant allergen ...substituting *any* amino acid residue of any B cell epitope at *any* position, (2) *any* allergen is derived from any pollen allergen, (3) *any* amino acid residue of B epitope or (4) *any* one patch is substituted, (5) *any* recombinant allergen derived from Poales, Asterales or Urticales, house dust mite allergen, mite allergen from Dermatophagoides, cockroach allergen, any allergen derived from any animal allergen, any animal allergen originating from cat, dog or horse, venom allergen, venom allergen originating from the taxonomic order of Hymenoptera, Vespidae, Apidae and Formicoide, or from Ves v5, (6) *any* pharmaceutical composition comprising *any* recombinant allergen, (7) *any* recombinant mutant allergen derived from *any* naturally occurring allergen for a pharmaceutical composition in the form of a vaccine against allergic reactions. Further, Applicant discloses only two recombinant mutant allergens; there is a lack of a written description of *any* additional representative species of recombinant allergen, or recombinant mutant allergen for a vaccine composition, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the

genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 2/27/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the instant application provides sufficient written description to inform the skilled artisan that the Applicants were in possession of the claimed invention as a whole at the time the application was filed. In the instant case, the specification provides a combination of chemical/physical and functional characteristics that show Applicants were in possession of the claimed invention (page 16-17 and 19-20).

However, the claims are drawn to *any* recombinant allergen from *any* one of the taxonomic orders such as Fagales, Hymernoptera and Dermatophagoides having *any* point mutation or *any* amino acid substitution in *any* patch of at least 15 amino acids in *any* undisclosed allergens from said taxonomic orders such as Fagales, Hymernoptera and Dermatophagoides.

The specification discloses only two recombinant allergens from birch pollen major allergen comprising SEQ ID NO: 37 from the taxonomic order of *Fagales* and vaspid venom Ves v 5 comprising SEQ ID NO: 38-39 from the taxonomic order of Hymenoptera. Further, there are no in vivo working examples demonstrating that any recombinant allergens or any recombinant modified allergen from any taxonomic orders are effective in prevent all allergy.

Other than the specific recombinant allergens mentioned above and such as the ones recited in claims 28 and 50, there is inadequate written description about any other recombinant allergen as set forth in claims 2-3, 5-9, 12-14, 19-26, 28-49, and 51 and any pharmaceutical composition comprising any recombinant allergen as set forth in claim 33-34. Further, Applicant discloses only two recombinant mutant allergens; there is a lack of a written description of *any* additional representative species of recombinant allergen, or recombinant mutant allergen for a vaccine composition, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

7. Claim 50 stands objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

11. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
May 19, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600